DESCRIPTION FOR THE GENERAL PUBLIC

The overarching goal of the project is to develop models of histamine receptors, which could be used as alternative tests in the screening of potential pharmaceutics. Presented aim of the project will be achieved by rational designing and synthesis of matrices of molecular receptors composed from *N*-lipidated peptides immobilized on a cellulose. The peptide fragment of molecular receptors will contain amino acid residues that are crucial for the native (H1-H4) histamine receptors binding pockets. Obtained matrices of molecular receptors will be used for studies of interactions of selected antagonist / agonist compounds with binding cavities of molecular receptor. The study should give rise to the knowledge playing a crucial impact on the strength and specificity of the interaction between pharmacologically active compounds and the receptor binding pockets of molecular receptors acting as a simplified models of histamine receptors. Studies should result the knowledge concerning relationship between the interaction's character of the pharmacologically active compounds and the structures of the receptor binding pockets, thereby defining a new relationship between the structure of the molecular receptor (the host) - structure of the pharmacologically active substance (guest) - stability of the molecular complex formed by guest and host and biological activity of the guest molecules. Correlating all these variables should result in the ability to identify the molecular receptors features determining the selectivity of interaction with agonist/antagonist molecules, which in turn should be transformed into the ability to construction of the new tools for preliminary screening of new drugs acting on histamine receptors. The overall objective of the project – achievement of a data set of interactions between binding cavities of molecular receptors and pharmacologically active compounds will be achieved by rational design of the structure of molecular receptors. Within the project it is planned the synthesis and application in the docking experiments of 5 matrices of molecular receptors: Matrix I build from amino acid residues D, (S, D, T, A) F responsible for binding of histamine, agonists and antagonists of H1-H4 receptors; Matrix II from amino acids present in conservative motif D (E) RY of transmembrane helix III; Matrix III from amino acids present in conservative motif CWxP of transmembrane helix VI; Matrix IV constructed with amino acids which are present in conservative motif NPxxY of transmembrane helix VII. The last stage of the study will include the designing and synthesis of Matrix V - which will form the simplified model of the natural receptors H1-H4. Typical procedure for docking comprises carrying out two parallel experiments: (1) docking a reporter compound; (2) docking a colorless ligand and subsequent competitive docking of the reporter dye. The difference in coloration is quantified and evaluated as affinity between colorless ligand and receptor. Correlations between the binding strength, structure of the ligand, and structure of molecular receptor will be determined using statistical and chemometric methods. From earlier work it is known that *N*-lipidated peptides immobilized on the cellulose via an aromatic linker are able for selective bindings of the various ligands. Binding cavities are formed by a self-organization of flexible peptide chains which due to conformational freedom are able to reshape the size and arrangement of functional group inside the docking pocket to become accustomised to requirements of the ligand. The interactions between molecular receptors and ligands are very selective. Molecular receptors are able to recognize even small changes in the structures of bound ligands. Preliminary results using the randomized matrix of molecular receptors indicate its capability to differentiate agonists from antagonists acting at histamine receptors. Efficient molecular recognition of ligands by the molecular receptors in the case of research on drug discovery is very important because the biological activity and different interaction with receptor can be determined even by small changes in the structure of ligands. All matrices of molecular receptors will be synthesized using SPOT automated peptide synthesizer. An automation of complex synthetic process ensure high reproducibility of results, increase the density of receptors on the surface and reduce amount of the ligands used in the studies. As a coupling reagents for peptide synthesis will be used very effective triazine coupling reagents ensuring a high efficiency of peptide bong formation and high efficiency of removal of side-products (elimination of deposites on the surface of a cellulose).

Apart from cognitive value of the project and acceleration of drug discovery research, the proposed solution provides full standardization and thus increase the reproducibility of the results. Developed matrices of molecular receptors may be a variant of the new research model that will simplify and reduce the costs of the initial phase of the search for new drugs by improving the measurement methodology used for monitoring of the host-guest interactions, and thus reduce the scope of the studies conducted on laboratory animals. The most important seems to be refinement of the models for testing of new candidates in preclinical phase, thus increasing the chance of success of these studies, accelerating the search phase, reducing its costs, and a risk of failure of pre- and clinical phases. It seems that once developed the research methodology, it can also be used to test other receptor proteins which are targets of pharmaceuticals. The results obtained during the project will contribute to the growth of innovation and the development of science in Poland and the development of science around the world.